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A Systematic Review of Phytochemical and Phytotherapeutic Characteristics of Bitter Almond

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ABSTRACT

Bitter almond is one of the medicinal plants that have been used to prevent and treat diseases since many centuries ago. Bitter almond essential oil can be effectively used to heal wounds, hemorrhoids and hair loss, relieve joint pain, facilitate delivery, and strengthen and condition hairs. Moreover, oral use of bitter almond seed has been demonstrated to cause antioxidant, antibacterial, and anticancer effects because of containing certain compounds such as amygdalin. However, there have been some challenges in investigations conducted to discover bitter almond-based oral, herbal drugs to treat different diseases such as cancer because of cyanide-induced poisoning, partly precluding use of this plant. This study was conducted to comprehensively review the traditional uses, phytochemical compounds, and therapeutic actions of bitter almond and its compound as well as the side effects due to use of them.

Key Words: Bitter almond, Amygdalin, Cancer, Antioxidant properties, Traditional medicine.

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INTRODUCTION

Worldwide, plants have long been used to treat many diseases [1]. The local people of different regions across the world have been using different parts of medicinal plants, as infusion, decoction, incense, and poultice to prevent and treat diseases [2-8]. In recent studies, the researchers, inspired by traditional uses of these plants, have examined their effects on many disorders [9-15]. The plants and their compounds, which demonstrated to have optimal actions, have been used to develop pharmaceutical products in modern medicine, because of several therapeutic effects and few side effects [16-26]. Medicinal plants are compatible with the body's immunity system because of being nature-based [27-30]. Almond is a plant-based product which is useful to human beings' health [31]. Almond tree is native to the Mediterranean region of Asia and has been cultivated in central and western Asia [32]. It may reach to a height of 6-8 m and belongs to family Rosaceae.

Almond has two varieties, non-bitter and bitter [32, 33]. Non-bitter almond (Sweet almond) is the fruit

of a tree called *Prunus amygdalus* var. *dulcis* with very low amounts of toxic phytochemicals. Bitter almond is the fruit of *Prunus amygdalus* var. *amara* that contains comparably greater amounts of toxic phytochemicals called glycoside amygdalin [34, 35], such that its excessive use (toxic tolerable doses for human being) can lead to poisoning and even death [36]. Bitter almond has pink shoots and relatively flatter and shorter fruits than non-bitter almond that has white shoots [37].

Although bitter almond has various health benefits [34], it has adverse and toxic effects on the body because of containing hydrocyanic acid which is the reason for the bitter taste of bitter almond [38, 39]. Many studies have been conducted to investigate the benefits of bitter almond to prevent and treat diseases.

Studies have demonstrated that use of bitter almond seed or essential oil can help to prevent stretch marks in pregnancy [40] and to inhibit tumor growth [41]. Moreover, almond seed extract exerts antioxidant and antibacterial properties [42]. However, according to



some studies, it cannot be definitely argued that oral use of bitter almond and the products derived from it causes anticancer actions [43, 44]. Regarding the traditional uses and therapeutic effects of bitter almond according to available evidence, and the lacking of comprehensive study on the therapeutic properties of bitter almond with regard to its compounds, we conducted this review article to explore the phytochemical and phytotherapeutic properties of bitter almond.

In this study, we searched for amygdalin, *Prunus amygdalus* var. amara and bitter almond, as search terms, in the abstracts of the articles indexed in PubMed till 30 March, 2016 using EndNote software and then retrieved articles with these two terms appearing in their abstracts. The abstracts were reviewed according to predetermined inclusion and exclusion criteria. The full texts of the articles were examined to assess study eligibility if needed. The articles without English abstracts as well as accessible English full texts were excluded. Only the articles that mainly investigated the phytotherapeutic effects and phytochemical compounds of bitter almond were included. Other materials related to the subject under study were manually searched for in reliable references in libraries.

Phytochemical characteristics

As with non-bitter almond, bitter almond kernel contains various nutrients such as minerals, vitamins, and fatty acids. The major bioactive components of bitter almond are prunasin, amygdalin, flavonoid and phenolic acids which exert anticancer and antioxidant effects. However, available information is inadequate about the pharmacokinetics of amygdalin and other compounds in bitter almond.

Nutritional value

Chemical composition of bitter almond can be detected by a variety of techniques such as inductively coupled plasma mass spectrometry (ICP-MS) [45]. The amount of nutrient in almond depends on the region of occurrence and species. In addition to fat and many amino acids, bitter almond contains minerals, such as Zn, Mg, Fe, Ca, and K, and vitamins, particularly vitamin E [46]. Bitter almond kernel contains approximately 48% fat, 30% protein, 60% carbohydrates, 3% amygdalin, and some other nutrients [47]. Moreover, according to Li et al study on bitter almond nutrients, bitter almond kernel contains 49.6% fat and 94.84% of its fatty acids were unsaturated. In addition, the kernel was found to contain 27% protein, 26.72% amino acids (17 amino acids in total), and 7.57% essential amino acids [48]. The major fatty acids of bitter almond kernel are oleic acid (70.61%) and linoleic acid (20.68%). Bitter almond kernel is considered a valuable source of lipid soluble vitamins [vitamin D (1.40 mg/kg), vitamin K (42.25 mg/kg) and saturated fatty acids (7.85 mg/kg), and unsaturated fatty acids (92.15 mg/kg)] [49]. Bitter almond has a large number of nutrients [35] However, use of excessive (more-than safe amounts) amounts of bitter almond, depending on age and body mass index,

can cause cyanide-induced complications in human [50].

Phytochemical investigations

Bitter almond has a unique smell due to 3-methylbutanal and 2-methylbutanal present in its seed [51]. Almond contains also polyphenolic compounds, especially flavonoids that exist in different organs [52, 53]. Flavonoid compounds, including myricetin, naringenin and kaempferol, and phenolic acids like vanillic acid, caffeic acid, ferulic acid, hydroxycinnamic acid, rosmarinic acid, and proanthocyanidin compounds are found in the extract of bitter almond. Moreover, bitter almond is a good natural source of phenolic compounds (674.40 mg GAE/g in total), phytosterols [stigmasterol (242.65 mg/kg), β -sitosterol (366.95 mg/kg), ergosterol (0.65 mg/kg), α -tocopherol (104.15 mg/kg), δ -tocopherol (4.95 mg/kg), and retinol (0.05 mg/kg)] [49]. Prunasin and amygdalin are the main compounds of bitter almond.

Prunasin is a cyanogenic monoglucoside found in many organs of almond [54]. To synthesize amygdalin, different concentrations of prunasin are required in fruit. The difference in these concentrations determines whether ripened almond is bitter or non-bitter [37]. A set of genes is involved in the development of different properties in bitter almond and sweet almond [55]. Prunasin forms at the beginning of fruit development and converts to diglucoside amygdalin throughout the process of nuclear development and maturation [56]. Prunasin lacks the second sugar in amygdalin structure that is present in green almond and is converted to amygdalin throughout the process of fruit ripening [39, 57]. At anthesis, the almond and the flax fruits contain the monoglucosides prunasin, and linamarin and lotaustralin, respectively, while, at maturity, only the corresponding diglucosides amygdalin, linustatin and neolinustatin are found, respectively [57].

Cyanide compounds differ in various organs of bitter almond tree. Dicenta et al investigated the cyanogenic compounds, amygdalin and prunasin, in kernel, leaves, and root of non-bitter, semi-bitter, and bitter almond trees. They found that prunasin existed only in the roots and leaves of all the studied genotypes and in all roots. But, only the genotypes of bitter almond are able to convert prunasin amygdalin in almond kernel [58]. In bitter almond, the beta-glucosidase activity was low in the inner epidermis in the tegument facing the nucellus. These data, taken together, show that in the bitter genotype, prunasin synthesized in the tegument is transferred into the cotyledon through the transfer cells and converted into amygdalin in the developing almond seed.

The prunasin turnover may offer a buffer supply of ammonia, aspartic acid, and asparagine that enables the plants to balance the supply of nitrogen to the developing cotyledons [39].

Cyanogenic glycosides are produced by many plants and produce cyanide hydrogen via hydrolysis [59]. This process is referred to as cyanogenesis which happens in bitter almond kernel [34]. Bitter almond

contains a cyanogenic diglucoside compound, amygdalin (D-mandelonitrile- β -gentiobioside) (Figure 1). Amygdalin is the cause of bitter taste of almond kernel [37, 58], and because amygdalin decomposes into cyanuric acid, its use can cause poisoning-induced complications and lead to death [60]. Amygdalin can produce certain substances such as glucose, benzaldehyde, and cyanide hydrogen through hydrolyzing an enzyme called β -glucosidases [39] or acid hydrolysis [50].

Amygdalin concentration varies depending on the species of almond and other factors. Amygdalin is also found in the other plants from family Rosaceae, such as peach and apricot. Studies indicate that the phenotype and the region of cultivation can affect the amount of amygdalin in kernel, such that amygdalin concentration is 2.16-157.44 mg/kg in non-bitter, 523.50-1772.75 mg/kg in semi-bitter, and 33006.60-53998.30 mg/kg in bitter almonds [61]. Moreover, amygdalin concentration increases as fruit develops [37]. Hydrocyanic acid concentration of bitter almond is approximately 40 times higher than that of non-bitter almond [34].

Phytotherapeutic properties

Traditional uses of bitter almond

Bitter almond is highly valuable in traditional and modern medicine [48]. In Iranian traditional medicine, bitter almond essential oil is used to treat burns and wounds and to protect stomach [62]. Moreover, according to Iranian traditional medicine, bitter almond ointment or essential oil is used to treat acne, joint pain, hair loss, to facilitate delivery, and to strengthen and condition hairs. In addition, the physicians of old Iran made a bitter almond-based remedy to treat hemorrhoids [63].

Antioxidant properties

Almond contains some phytochemicals with antioxidant properties [52]. Flavonoid and phenolic compounds are accumulated in 15.198 mg/g in bitter almond skin and kernel [53]. Some studies extensively investigating the antioxidant properties and compounds of bitter almond, demonstrated that bitter almond extract contains flavonoid (22.98 mg/g in total), suggesting the kernel of bitter almond has great antioxidant properties [49]. In Gomaa study [42], mean antioxidant capacity of aqueous, methanolic, and ethanolic extracts was derived 56.72, 44.86, and 33.05 mg/g dry extract, respectively. In addition, the highest amount of phenolic compounds was reported to exist in aqueous extract and the highest amount of flavonoid compounds and lycopene in the ethanolic extract of bitter almond kernel. Moreover, bitter almond is rich in fat soluble vitamins. Vitamin E is one of the vitamins that can exert optimal antioxidant effects and is found abundantly in the seed kernel of this plant [49].

Anticancer properties

Amygdalin, one of the most important compounds of bitter almond, was referred to as B17 or laetrile in the last decades and has been known to be a unique substance to treat cancer for over 100 years [64].

Cyanide in laetrile or chemically referred to as amygdalin is thought to be the cause of anticancer properties that can contribute to treating different cancers [65] (Table 1). Amygdalin was considered an unconventional but desired anticancer agent in 1970s [66]. Gomaa study demonstrated that aqueous, methanolic, and ethanolic extracts of bitter almond kernel can inhibit the growth of cancer cell lines HepG2, HCT-116, and MCF-7 in a dose-dependent manner with different susceptibilities among these cell lines [42]. A study on amygdalin effect on the growth of a number of cancer cell lines indicated that amygdalin might inhibit tumor growth by down-modulating cdk2 and cyclin in vitro [41].

Furthermore, anticancer effects of amygdalin have been investigated on hepatocarcinoma and colon, bladder, and cervical cancers [67-72]. The findings demonstrated that amygdalin is an anticancer agent that can induce apoptosis and inhibit adhesion of cells [73]. Moreover, amygdalin can be used as a chemopreventive agent to prevent or alleviate progression of cancers.

Besides that, Qian et al reported the anti-metastatic properties of amygdalin in lung cancer patients. They indicated that low doses of amygdalin had weaker inhibitory effects on cancer cells and this effect on the cells increased with increase in the administered dose [68] (Table 1). However, increased doses are more likely to cause cyanide-induced poisoning.

In this regard, a review article published in 2011 reported that laetrile or amygdalin could not be much useful to treat cancer patients because the risk of cyanide-induced poisoning due to amygdalin especially if amygdalin is administered orally [74]. Besides that, a study on clinical benefits of amygdalin did not strongly suggest that amygdalin be used as an anticancer drug in the light of its benefits vs. the risks potentially induced by it [70].

Despite of previous studies for evaluating the effects of bitter almond and its compounds on cancers, there is still debate about anticancer effects of amygdalin because this compound has not yet been adequately investigated in clinical trials [65]. Cyanide compounds can cause cell necrosis through antibody-guided enzyme nitrile therapy, such that enzymatic catalysis of the substrate generates cyanide, a metabolic poison that asphyxiates cells and causes a necrotic-like cell death. This system is referred to as antibody-guided enzyme nitrile therapy [76]. Moreover, these compounds may cause intracellular hypoxia through reversibly binding to mitochondrial c cytochrome C oxidase, the terminal enzyme in the mitochondrial respiration chain, and suspend adenosine triphosphate synthesis, and consequently lead to cell suffocation and death [77, 78]. However, it can be definitely argued that amygdalin, present in bitter almond, can exert considerable anticancer effects on different cancer cells through certain mechanisms such as inhibition of cell cycle and induction of apoptotic and anti-metastatic actions. But, anticancer effects of bitter almond have been less frequently studied in animals and humans

because large amounts of this plant may lead to cyanide-induced poisoning because of containing large amounts of amygdalin [79]. FDA has banned amygdalin use since 1980 and European countries have prohibited its sale [69]. However, amygdalin is still being used as an anticancer agent in some regions worldwide [80, 81]. Therefore, it is essential to investigate the effect of amygdalin on normal cells death and then in laboratory animals to find a dose with anticancer effects but without fatal effects on normal cells and non toxic to humans.

Prevention of stretch marks

In pregnancy, mechanical tension can damage the connective tissue of the dermis, and plant-based oils can play a preventive role in this condition [82]. Massaging with bitter almond essential oil can help to prevent stretch marks, but the evidence is weak on the effect of bitter almond essential oil or other bitter almond-based products in preventing stretch marks or alleviating its severity [44]. To the best of our knowledge, only one study demonstrated that 15-min massaging with bitter almond essential oil prevented

the progression of stretch marks. However, this oil exerted no therapeutic effects [40].

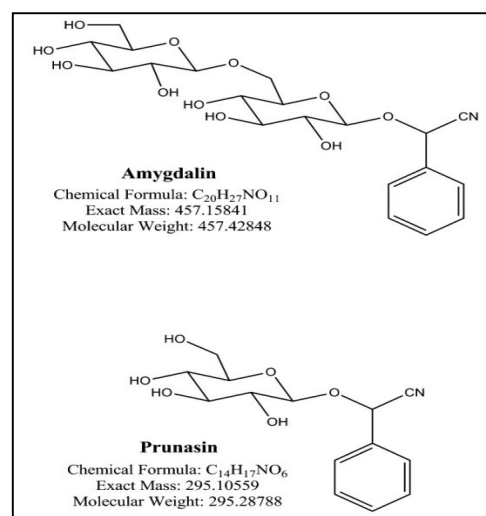


Figure 1. Chemical structure of amygdalin and prunasin, reproduced from [25].

Table 1. Anticancer properties of bitter almond and amygdalin

Type of cancer	Type of extract/ Active compound	Dosage	Main results	Ref.
Colon cancer	Amygdalin	0.25-5 mg/ml	Down-regulation of cell cycle-related genes in SNU-C4 human colon cancer cells.	[71]
Breast cancer		2.5-80 mg/mL	Amygdalin inhibited proliferation of MCF7, MDA-MB-231, and Hs578T cells (IC50 values of amygdalin in MCF7, MDA-MB-231, and Hs578T cells were 30.8, 48.5 and 52.9 mg/mL, respectively); regulated apoptosis-related proteins and signaling molecules; also inhibited adhesion of Hs578T cells.	[72]
Bladder Cancer		1.25-10 mg/ml	Amygdalin reduced growth and proliferation in a dose-dependent manner in all studied bladder cancer cell lines by delaying cell cycle progression and G0/G1 arrest.	[41]
Cervical cancer		1.25-20 mg/mL	Inhibited the growth of HeLa cell xenografts through a mechanism of apoptosis.	[73]
Prostate cancer		0.01-10 mg/ml	Induced apoptotic cell death in human DU145 and LNCaP prostate cancer cells by caspase-3 activation through down-regulation of Bcl-2 and up-regulation of Bax.	[65]
Lung cancer	Aqueous extract Ethanol extract Aqueous extract Methanolic extract Ethanol extract	2.5-5 mg/ml	Amygdalin was likely to have anti-metastatic NSCLC effect.	[68]
Breast carcinoma cell line (MCF-7)		1.56-50 µg/ml	Cytotoxicity activity (IC50= 29.5 µg)	[42]
Colon carcinoma cell line (HCT-116)			Cytotoxicity activity (IC50= 31.4 µg)	
Hepatocellular carcinoma cell line (Hep-G2)			Cytotoxicity activity (IC50= 24.5 µg)	
			Cytotoxicity activity (IC50= 45.7 µg)	
			Cytotoxicity activity (IC50= 39.4 µg)	

Table 2. Antibacterial properties of bitter almond extract

Type of Microorganism	Extract type	Minimum inhibitory concentration (MIC)
<i>Bacillus subtilis</i> ATCC 6633	Aqueous	2.5 mg/ml
	Methanolic	0.625 mg/ml
	Ethanol	2.5 mg/ml
<i>Staphylococcus aureus</i> NCTC 7447	Methanolic	1.25 mg/ml
	Ethanol	10 mg/ml
<i>Salmonella typhi</i> NCIMB 9331	Methanolic	5 mg/ml

The reviewed studies indicate that bitter almond essential oil can be used to prevent stretch marks. This may be explained by the fact that almond kernel contains large amounts of fat soluble vitamins such as vitamin E, because vitamin E, a strong antioxidant, contributes significantly to reducing the extent and

severity of skin pathological complications [83]. Consistent with this argument, some studies reported vitamin E-contained emulsions and creams to be effective in preventing and relieving stretch marks [84]. Moreover, the presence of flavonoids and phenolic compounds, as antioxidant compounds, in bitter almond confirms prophylactic and relieving effects on stretch marks-induced skin complications. However, the therapeutic effects of these compounds have not yet been confirmed.

Antimicrobial properties

Investigations on antibacterial properties of bitter almond indicate that the extract of bitter almond seed is effective in decreasing *Bacillus cereus* colonies and tracing the active toxin of this bacterium in foods. This effect is reinforced if bitter almond is combined with

other plants such as green tea [85]. Different extracts of bitter almond can exert different antimicrobial effects. Of these extracts, methanolic extract was found to exert more optimal effects on *Bacillus subtilis* and *Staphylococcus aureus* [42](Table 2). Few studies have yet confirmed the antimicrobial effects of bitter almond. Moreover, the studied extracts were found to be effective on a limited number of bacteria, or were not able to exert optimal inhibitory effects on at least a specific bacterium. Comprehensive studies are needed to determine the minimum bactericidal concentration (MBC) of bitter almond extracts on bacteria.

Side effects

Many people around the world are accidentally poisoned by plant-based cyanide compounds [34]. The fruits and kernel of different species of almond can produce these compounds. The amounts of cyanide compounds are much higher in *P. amygdalus* amara than other varieties of *P. amygdalus* [86]. For this reason, the breath of patients with cyanide-induced poisoning has a bitter almond-like odor[87].

Normally, blood cyanide concentration is lower than 0.2 mg/L [88]. People with blood cyanide concentrations of ≥ 1 mg/L and plasma lactate concentrations of ≥ 72 mg/dL are considered to be patients with suspected cyanide poisoning [89]. However, it is difficult to determine exactly which amounts of bitter almond, if used, lead to poisoning [86]. Cyanide-induced poisoning due to bitter almond may cause certain complications such as sudden headache, dizziness, vomiting, bradycardia, severe lactic acidosis, acidosis, hypotension, liver damage, walking, fever, seizure, and coma [65, 88]. The action mechanism of these complications is that cyanide causes intracellular hypoxia by reversibly binding to mitochondrial cytochrome oxidase a3 inside the mitochondria. Cytochrome oxidase a3 is necessary to reduce oxygen to water in the fourth complex of oxidative phosphorylation. Cyanide binding to the ferric ion in cytochrome oxidase a3 inhibits the terminal enzyme in the respiratory chain and stops electron transport and oxidative phosphorylation [77]. Cyanide-induced poisoning due to high doses of bitter almond requires both invasive and support treatments to prevent death[50]. Processing plant dissections is an effective approach to reduce plant-induced toxicity. For example, thermal processing can stop the enzymatic activity of cyanogenic glycoside-contained bitter almond and hence reduce its toxicity [90].

CONCLUSION

Many studies on the properties of bitter almond and amygdalin have been conducted in vitro and in vivo. To the best of our knowledge, no randomized clinical trials have yet been conducted because of potential cyanide-induced poisoning due to amygdalin. Therefore, reliable findings on this subject are not available, precluding arriving at definite conclusions about use of bitter almond kernel. However, in the light of the valuable compounds present in bitter

almond, and their optimal antioxidant and anticancer effects and since these antioxidant compounds play a highly important role in treating cancer through preventing oxidative stress, then future studies are recommended to investigate the action mechanisms of anticancer effects of bitter almond and amygdalin, the most important compound of this plant, in animal models to find non toxic and therapeutically efficient doses. Next, these doses can be studied in clinical trials to treat different cancers.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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